

In the Claims

The following amendments are made with respect to the claims in the International application PCT/EP2005/000604.

This listing of claims will replace all prior versions and listings of claims in this application.

38 (new). A polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide.

39 (new). The polynucleotide of claim 38, wherein the modified EGF has at least wild-type EGFR binding activity.

40 (new). The polynucleotide of claim 38, which is DNA, genomic DNA or RNA.

41 (new). A vector comprising a polynucleotide selected from the group consisting of: (a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide.

42 (new). The vector of claim 41 in which the polynucleotide is operatively linked to expression control sequences allowing expression in a prokaryotic and/or eukaryotic host cell.

43 (new). A host cell genetically engineered to comprise a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide.

44 (new). A method for producing a modified EGF encoded by a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide;

wherein said method comprises: culturing a host cell that has been genetically engineered to comprise said polynucleotide and recovering the modified EGF encoded by said polynucleotide.

45 (new). A process for producing cells capable of expressing modified EGF comprising genetically engineering cells *in vitro* with a vector comprising a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF

with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide.

46 (new). A modified EGF having an amino acid sequence encoded by a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide; or which is obtainable by a method for producing a modified EGF encoded by said polynucleotide;

wherein said method comprises: culturing a host cell that has been genetically engineered to comprise said polynucleotide and recovering the modified EGF encoded by said polynucleotide.

47 (new). The modified EGF of claim 46 or a fusion polypeptide thereof coupled to at least one chemical moiety.

48 (new). The modified EGF or fusion polypeptide of claim 47, wherein the chemical moiety is selected from the group consisting of spacers, markers, tags, lipids, drugs, capping groups, polypeptides and spacers attached to a second chemical moiety.

49 (new). The modified EGF or fusion polypeptide of claim 48, wherein the polypeptide is selected from the group consisting of cytokines, chemokines, growth factors, adhesion molecules, antibody light and/or heavy chains, single chain antibodies, toxins, enzymes, receptor ligands, lytic peptides, membrane insertion sequences and fluorescent proteins or fragments thereof.

50 (new). The modified EGF or fusion polypeptide of claim 48, wherein the spacer is selected from the group consisting of bifunctional polyethyleneglycol and derivatives thereof, oligopeptides comprising between 1 to 40 natural or synthetic amino acids, 8-amino-3, 6-dioxatanoic acid (doo), and (doo)<sub>n</sub>, with n= 2-10.

51 (new). The modified EGF or fusion polypeptide of claim 48, wherein the marker is selected from the group consisting of electron dense molecules, paramagnetic molecules, superparamagnetic molecules, radioactive molecules, non-radioactive isotopes, and fluorescent molecules.

52 (new). The modified EGF or fusion polypeptide of claim 48, wherein the lipid is selected from the group consisting of glycerides, glycerophospholipids, glycerophosphinolipids, glycerophosphono-lipids, sulfolipids, sphingolipids, phospholipids, isoprenolides, steroids, stearines, sterols, and carbohydrate containing lipids.

53 (new). The modified EGF or fusion polypeptide of claim 52, wherein the phospholipid is selected from the group consisting of phosphatidylcholine (PC), phosphatidylserine (PS), and phosphatidylethanolamine (PE).

54 (new). The modified EGF or fusion polypeptide of claim 48, wherein the lipid is selected from the group consisting of N-caproylamine-PE, N-dodecanylamine-PE, phosphatidylthio-ethanol, N-[4-(p-maleimidomethyl)cyclohexane-carboxamide-PE (N-MCC-

PE), N-[4-(p-maleimidophenyl)butyramide]-PE (N-MPB), N-[3-(2-pyridyldithio)propionate]-PE (N-PDP), N-succinyl-PE, N-glutaryl-PE, N-dodecanyl-PE, N-biotinyl-PE, N-biotinyl-cap-PE, phosphatidyl-(ethylene glycol), PE-polyethylene glycol (PEG)-carboxylic acid, PE-PEG-maleimide, PE-PEG-PDP, PE-PEG-amine, PE-PEG-biotin, PE-PEG-HNS, dipalmitoyl-glycerolsuccinyl-lysine, alpha-methoxy-omega-(1,2-dioctadecenoyloxy glyceryl) (DO), alpha-methoxy-omega-(1,2-ditetradecenoyloxy glyceryl) (DT).

55 (new). The modified EGF or fusion polypeptide of claim 48, wherein the second chemical moiety is selected from the group consisting of drugs, markers, tags, polypeptides and lipids.

56 (new). A composition comprising a modified EGF, or a fusion polypeptide thereof, having the amino acid sequence encoded by a polynucleotide selected from the group consisting of:

- (a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;
- (b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;
- (c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;
- (d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and
- (e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide; or which is obtainable by a method for producing a modified EGF encoded by said polynucleotide;

wherein said method comprises: culturing a host cell that has been genetically engineered to comprise said polynucleotide and recovering the modified EGF encoded by said polynucleotide; and wherein said composition comprises at least one further

component selected from the group consisting of liposomes, virosomes, microspheres, niosomes, dendrimers, stabilizers, buffers excipients and additives.

57 (new). The composition of claim 56, wherein the polypeptide is integrated into or attached to a liposome, microsphere, niosome, dendrimer, or virosome.

58 (new). The composition of claim 56, further comprising a drug selected from the group consisting of analgesics, antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics, antiinfectives, antidemenics (nootropics), antidiabetics, antidotes, antiemetics, antivertiginosics, antiepileptics, antihemorrhagics, antihypertotics, antihypotonics, anticoagulants, antimycotics, antitussiv agents, antiviral agents, beta-receptor and calcium channel antagonists, broncholytic and antiasthmatic agents, chemokines, cytokines, mitogens, cytostatics, cytotoxic agents and prodrugs thereof, dermatics, hypnotics and sedatives, immunosuppressants, immunostimulants, and peptide or protein drugs or their respective prodrugs.

59 (new). The composition of claim 58, wherein the cytostatic and cytotoxic drug are selected from the group consisting of alkylating substances, anti-metabolites, antibiotics, epothilones, anti-androgens, anti-estrogens, platinum compounds, hormones and anti-hormones, interferons and inhibitors of cell cycle-dependent protein kinases (CDKs), platine coordination complexes ethyleneimenes, methylmelamines, trazines, vinca alkaloids, pyrimidine analogs, purine analogs, alkylsulfonates, folic acid analogs, anthracendiones, substituted urea, methylhydrazin derivatives, in particular acediasulfone, aclarubicine, ambazone, aminoglutethimide, L-asparaginase, azathioprine, bleomycin, busulfan, calcium folinate, carboplatin, carpecitabine, carmustine, chlorambucil, cis-platin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin dapsone, daunorubicin, dibrompropamide, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, epothilone B, epothilone D, estramucin phosphate, estrogen, ethinylestradiol, etoposide, flavopiridol, floxuridine, fludarabine, fluorouracil, fluoxymesterone, flutamide fosfestrol, furazolidone, gemcitabine, gonadotropin releasing hormone analog, hexamethylmelamine, hydroxycarbamide, hydroxymethylnitrofurantoin, hydroxyprogesteronecaproat, hydroxyurea, idarubicin, idoxuridine, ifosfamide, interferon  $\alpha$  irinotecan, leuprolide, lomustine, lurtotecan, mafenide sulfate olamide, mechlorethamine, medroxyprogesterone acetate, megastrolacetate,

melphalan, mepacrine, mercaptopurine, methotrexate, metronidazole, mitomycin C, mitopodozide, mitotane, mitoxantrone, mithramycin, nalidixic acid, nifuratel, nifuroxazide, nifuralazine, nifurtimox, nimustine, ninorazole, nitrofurantoin, nitrogen mustards, oleomucin, oxolinic acid, pentamidine, pentostatin, phenazopyridine, phthalylsulfathiazole, pipobroman, prednimustine, prednisone, preussin, procarbazine, pyrimethamine, raltitrexed, salazosulfapyridine, scriflavinium chloride, semustine streptozocine, sulfacarbamide, sulfacetamide, sulfachlopyridazine, sulfadiazine, sulfaguanole, sulfamethizole, sulfamthoxazole, co-trimoxazole, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfathiazole, sulfisomidine, tamoxifen, taxol, teniposide, tertiposide, testolactone, testosteronepropionate, thioguanine, thiotepa, tinidazole, topotecan, triaziquone, treosulfan, trimethoprim, trofosfamide, vinblastine, vincristine, vindesine, vinblastine, vinorelbine, and zorubicin, or their respective derivatives or analogs thereof.

60 (new) A method for the treatment of a disease selected from the group consisting of proliferative diseases, immune diseases, infectious diseases, vascular diseases, rheumatoid diseases, and diseases, in which cells in or adjacent to the disease site show an increased expression of EGFR, wherein said method comprises administering, to a patient in need of such treatment, a modified EGF having an amino acid sequence encoded by a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode

a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide;

or which is obtainable by a method for producing a modified EGF encoded by said polynucleotide;

wherein said method comprises: culturing a host cell that has been transformed to comprise said polynucleotide and recovering the modified EGF encoded by said polynucleotide.

61 (new). The method of claim 60, wherein the proliferative disease is selected from the group consisting of lung cancer, liver cancer, head and neck cancer, bladder cancer, prostate cancer, cervix cancer, endometrial cancer, colorectal adenoma and adenocarcinoma, gastric cancer, oesophageal cancer, breast cancer, squamous carcinoma, glioblastomas and other high-grade primary brain tumors, chronic inflammatory proliferative diseases, vascular proliferative diseases and virus-induced proliferative diseases.

62 (new). A method for the diagnosis of a disease selected from the group consisting of proliferative diseases, immune diseases, infectious diseases, vascular diseases, rheumatoid diseases, and disease, in which cells in or adjacent to the disease site show an increased expression of EGFR, wherein said method comprises the use of a modified EGF having an amino acid sequence encoded by a polynucleotide selected from the group consisting of:

(a) polynucleotides encoding at least the mature modified epidermal growth factor (EGF) having the amino acid sequence as shown in one of SEQ ID NOs 1-15;

(b) polynucleotides having the coding sequence, as shown in one of SEQ ID NOs: 16-30 encoding at least the mature modified EGF;

(c) polynucleotides encoding a fragment or derivative of a mature modified EGF encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said mature modified EGF with the proviso that polypeptide positions 28 and 48 are not Lys, and said fragment or derivative has epidermal growth factor receptor (EGFR) binding activity;

(d) polynucleotides which are at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which encode a modified EGF having EGFR binding activity; and

(e) polynucleotides, the complementary strand of which hybridizes, under stringent conditions, to a polynucleotide as defined in any one of (a) to (d) and which encode

a modified EGF having EGFR binding activity; or the complementary strand of such a polynucleotide; or which is obtainable by a method for producing a modified EGF encoded by said polynucleotide;

wherein said method comprises: culturing a host cell that has been genetically modified to comprise said polynucleotide and recovering the modified EGF encoded by said polynucleotide.

63 (new). A method for producing a modified binding polypeptide, which is suitable for site-directed coupling, comprising the step of:

modifying a polynucleotide encoding the binding polypeptide, which is to be modified, by identifying within the reading frame of the polynucleotide all codons with the sequence:

a) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG;

b) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG and all codons with the sequence CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg and replacing any such codon with the condon NNN excluding CGT, CGC, CGA, CGG, AGA, and AGG;

c) GAT and GAC encoding Asp and replacing any such codon with the codon NNN excluding GAT and GAC and all codons with the sequence GAA and GAG encoding Glu and replacing any such codon with the codon NNN excluding GAA and GAG;

d) TGT and TGC encoding Cys and replacing all but one of such codons with the codon NNN excluding TGT and TGC;

e) TCT, TCC, TCA, TCG, AGT, and AGC encoding Ser and replacing all but one of such codons with the codon NNN excluding TCT, TCC, TCA, TCG, AGT and AGC and all codons with the sequence ACT, ACC, ACA and ACG encoding Thr and replacing all but one of such codons with the codon NNN excluding ACT, ACC, ACA and ACG;

f) ATG encoding Met and replacing all but one of such codons with the codon NNN excluding ATG;

g) TAT and TAC encoding Tyr and replacing all but one of such codons with the codon NNN excluding TAT and TAC;

h) TGG encoding Trp and replacing all but one of such codons with the codon NNN excluding TGG; and/or

i) CAT and CAC encoding His and replacing all but one of such codons with the codon NNN excluding CAT and CAC;  
wherein N is A, C, G or T.

64 (new). The method of claim 63, wherein all codons with the sequence

j) AAA and AAG encoding Lys are replaced with a sequence selected from the group consisting of BNK, NNT, NBK, NBK, KNK, NHT, BHK, DNT, VVT, HHT, VRT, HMT, TDK, BWT, TKK, TWC, KMT, AVT, and TWC;

k) AAA and AAG encoding Lys and CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg are replaced with a sequence selected from the group consisting of NHT, KNK, BHK, DNT, HHT, NWT, HMT, TDK, BWT, TKK, KMT, and TWC;

l) AAA and AAG encoding Lys are replaced with a sequence selected from the group consisting of BNK, NNT, NBK, NBK, KNK, NHT, BHK, DNT, VVT, HHT, VRT, HMT, TDK, BWT, TKK, TWC, KMT, AVT, and TWC and all codons with the sequence CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg are replaced with a sequence selected from the group consisting of NHK, NHT, KNK, BHK, DNT, HHT, NWT, HMT, BWT, TDK, TKK, RAK, and TWC;

m) GAT and GAC encoding Asp and GAA and GAG encoding Glu are replaced with a sequence selected from the group consisting of HNK, NBK, MNK, HHT, MRK, TKK, and TWC;

n) TGT and TGC encoding Cys are replaced all but one of with a sequence selected from the group consisting of VNK, NHK, NNG, VVK, BHK, MNK, VVT, NWT, RRK, VRT, MRK, BWT, NKT, RAK, RRG, KMT, AVT, and RAG;

o) TCT, TCC, TCA, TCG, AGT, and AGC encoding Ser and ACT, ACC, ACA and ACG encoding Thr are replaced all but one of with a sequence selected from the group consisting of RAK, TDK, TKK, VWT, BWT, NWT, RRG, and TWC;

p) ATG encoding Met are replaced all but one of with a sequence selected from the group consisting of NVK, BNK, NNT, VVK, NHT, KNK, BHK, DNT, VVT, HHT, NWT, RRK, VRT, HMT, MRK, TDK, BWT, TKK, RAK, RRG, TWC, and RAG;

q) TAT and TAC encoding Tyr are replaced all but one of with a sequence selected from the group consisting of VNK, NNG, VVK, MNK, VVT, RRK, MRK, VRT, TKK, RAK, RRG, AVT, and RAG;

r) TGG encoding Trp are replaced all but one of with a sequence selected from the group consisting of VNK, NHK, NNT, VVK, BHK, MNK, VVT, NWT, RRK, VRT, MRK, BWT, RAK, RRG, AVT, TWC, and RAG; and/or

s) CAT and CAC encoding His are replaced all but one of with a sequence selected from the group consisting of NNG, NBK, NBK, RRK, TDK, TKK, RAK, RRG, KMT, AVT, TWC, and RAG;

wherein R is A or G; K is G or T; M is A or C; W is A or T; B is C, G or T; D is A, G or T; H is A, C or T; V is A, G, or C; N is A, C, G or G.

65 (new). The method of claim 63, further comprising the step of coupling the modified polynucleotide to at least one additional polynucleotide encoding a polypeptide to produce a polynucleotide encoding a modified fusion polypeptide.

66 (new). The method of claim 63, further comprising the step of expressing the modified polynucleotide to produce a modified binding polypeptide or modified binding fusion polypeptide.

67 (new). The method of claim 66, further comprising the steps of:

a) incubating the modified binding polypeptide or fusion polypeptide or viral particles or cells displaying the modified binding polypeptide or fusion polypeptide with at least one binding partner of the binding polypeptide, and

b) selecting the modified binding polypeptide or fusion polypeptides or viral particles or cells displaying the modified binding polypeptide or fusion polypeptide, which shows at least 10% of the binding strength of the binding polypeptide to the binding partner.

68 (new). The method of claim 63, further comprising the step of site specific coupling of the modified binding polypeptide or fusion polypeptide to at least one chemical moiety.

69 (new). The method of claim 68, wherein the chemical moiety is coupled to

a) a N-terminal amino group of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG; and/or

ii) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG and all codons with the sequence CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg and replacing any such codon with the condon NNN excluding CGT, CGC, CGA, CGG, AGA, and AGG;  
and/or wherein all codons with the sequence:

iii) AAA and AAG encoding Lys are replaced with a sequence selected from the group consisting of BNK, NNT, NBK, NBK, KNK, NHT, BHK, DNT, VVT, HHT, VRT, HMT, TDK, BWT, TKK, TWC, KMT, AVT, and TWC;

iv) AAA and AAG encoding Lys and CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg are replaced with a sequence selected from the group consisting of NHT, KNK, BHK, DNT, HHT, NWT, HMT, TDK, BWT, TKK, KMT, and TWC; and/or

v) AAA and AAG encoding Lys are replaced with a sequence selected from the group consisting of BNK, NNT, NBK, NBK, KNK, NHT, BHK, DNT, VVT, HHT, VRT, HMT, TDK, BWT, TKK, TWC, KMT, AVT, and TWC and all codons with the sequence CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg are replaced with a sequence selected from the group consisting of NHK, NHT, KNK, BHK, DNT, HHT, NWT, HMT, BWT, TDK, TKK, RAK, and TWC;

b) a C-terminal carboxyl group of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) GAT and GAC encoding Asp and replacing any such codon with the codon NNN excluding GAT and GAC and all codons with the sequence GAA and GAG encoding Glu and replacing any such codon with the codon NNN excluding GAA and GAG; and/or wherein all codons with the sequence:

ii) GAT and GAC encoding Asp and GAA and GAG encoding Glu are replaced with a sequence selected from the group consisting of HNK, NBK, MNK, HHT, MRK, TKK, and TWC;

c) a newly added Cys residue of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) TGT and TGC encoding Cys and replacing all but one of such codons with the codon NNN excluding TGT and TGC;

and/or wherein all codons with the sequence:

ii) TGT and TGC encoding Cys are replaced all but one with a sequence selected from the group consisting of VNK, NHK, NNG, VVK, BHK, MNK, VVT, NWT, RRK, VRT, MRK, BWT, NKT, RAK, RRG, KMT, AVT, and RAG;

d) a newly added Ser residue of the modified binding of polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) TCT, TCC, TCA, TCG, AGT, and AGC encoding Ser and replacing all but one of such codons with the codon NNN excluding TCT, TCC, TCA, TCG, AGT and AGC and all codons with the sequence ACT, ACC, ACA and ACG encoding Thr and replacing all but one of such codons with the codon NNN excluding ACT, ACC, ACA and ACG;

and/or wherein all codons with the sequence:

ii) TCT, TCC, TCA, TCG, AGT, and AGC encoding Ser and ACT, ACC, ACA and ACG encoding Thr are replaced all but one of with a sequence selected from the group consisting of RAK, TDK, TKK, VWT, BWT, NWT, RRG, and TWC;

e) a newly added Met residue of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) ATG encoding Met and replacing all but one of such codons with the codon NNN excluding ATG;

and/or wherein all codons with the sequence:

ii) ATG encoding Met are replaced all but one of with a sequence selected from the group consisting of NVK, BNK, NNT, VVK, NHT, KNK, BHK, DNT, VVT, HHT, NWT, RRK, VRT, HMT, MRK, TDK, BWT, TKK, RAK, RRG, TWC, and RAG;

f) a newly added Tyr residue of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) TAT and TAC encoding Tyr and replacing all but one of such codons with the codon NNN excluding TAT and TAC;

and/or wherein all codons with the sequence:

ii) TAT and TAC encoding Tyr are replaced all but one of with a sequence selected from the group consisting of VNK, NNG, VVK, MNK, VVT, RRK, MRK, VRT, TKK, RAK, RRG, AVT, and RAG;

g) a newly added Trp residue of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) TGG encoding Trp and replacing all but one of such codons with the codon NNN excluding TGG;

and/or wherein all codons with the sequence:

ii) TGG encoding Trp are replaced all but one of with a sequence selected from the group consisting of VNK, NHK, NNT, VVK, BHK, MNK, VVT, NWT, RRK, VRT, MRK, BWT, RAK, RRG, AVT, TWC, and RAG; and/or

h) a newly added His residue of the modified binding polypeptide or fusion polypeptide and wherein the modified binding polypeptide has been modified by identifying within the reading frame of the polynucleotide all codons with the sequence:

i) CAT and CAC encoding His and replacing all but one of such codons with the codon NNN excluding CAT and CAC;

and/or wherein all codons with the sequence:

ii) CAT and CAC encoding His are replaced all but one of with a sequence selected from the group consisting of NNG, NBK, NBK, RRK, TDK, TKK, RAK, RRG, KMT, AVT, TWC, and RAG;

wherein N is A,C,G or T.

70 (new). The method of claim 68, wherein the chemical moiety is selected from the group consisting of spacers, markers, tags, lipids, drugs, capping groups, polypeptides and spacers attached to a second chemical moiety.

71 (new). The method of claim 70, wherein the polypeptide is selected from the group consisting of cytokines, chemokines, growth factors, adhesion molecules, antibody light and/or heavy chains, single chain antibodies, toxins, enzymes, receptor ligands, lytic peptides, membrane insertion sequences and fluorescent proteins or fragments thereof.

72 (new). The method of claim 63, wherein the binding polypeptide is selected from the group consisting of growth factors cytokines; chemokines; peptide hormones; adhesion molecules; viral coat proteins; and bacterial surface proteins.

73 (new). A method for the prevention, treatment or diagnosis of a disease, which is characterized by an increased or decreased amount of at least one binding partner of the binding polypeptide in diseased tissue or cells involved in the disease, wherein said method comprises the use of a modified binding polypeptide or fusion polypeptide producible by a method comprising the step of:

modifying a polynucleotide encoding the binding polypeptide, which is to be modified, by identifying within the reading frame of the polynucleotide all codons with the sequence:

a) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG;

b) AAA and AAG encoding Lys and replacing any such codon with the codon NNN excluding AAA and AAG and all codons with the sequence CGT, CGC, CGA, CGG, AGA, and AGG encoding Arg and replacing any such codon with the condon NNN excluding CGT, CGC, CGA, CGG, AGA, and AGG;

c) GAT and GAC encoding Asp and replacing any such codon with the codon NNN excluding GAT and GAC and all codons with the sequence GAA and GAG encoding Glu and replacing any such codon with the codon NNN excluding GAA and GAG;

d) TGT and TGC encoding Cys and replacing all but one of such codons with the codon NNN excluding TGT and TGC;

e) TCT, TCC, TCA, TCG, AGT, and AGC encoding Ser and replacing all but one of such codons with the codon NNN excluding TCT, TCC, TCA, TCG, AGT and AGC and all codons with the sequence ACT, ACC, ACA and ACG encoding Thr and replacing all but one of such codons with the codon NNN excluding ACT, ACC, ACA and ACG;

f) ATG encoding Met and replacing all but one of such codons with the codon NNN excluding ATG;

g) TAT and TAC encoding Tyr and replacing all but one of such codons with the codon NNN excluding TAT and TAC;

h) TGG encoding Trp and replacing all but one of such codons with the codon NNN excluding TGG; and/or

i) CAT and CAC encoding His and replacing all but one of such codons with the codon NNN excluding CAT and CAC;  
wherein N is A, C, G or T.

74 (new). The method according to claim 73, wherein the disease is selected from the group consisting of proliferative diseases, immune diseases, infectious diseases, vascular diseases and rheumatoid diseases.